

PCT/EP2004/052201

AMENDED CLAIMS

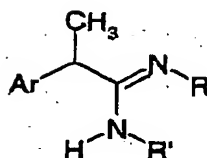
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CLAIMS

IAP20 Rec'd PCT/PTO 21 FEB 2006

1. Amidines of formula (I)



(I)

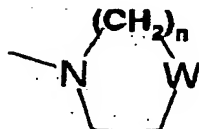
and pharmaceutically acceptable salts thereof,

wherein Ar is selected from:

3'-benzoylphenyl, 3'-(4-chloro-benzoyl)-phenyl, 3'-(4-methyl-benzoyl)-phenyl, 3'-acetylphenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxypheyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetilamino-phenyl, 4'-propionylamino-phenyl, 4'-benzoylamino-phenyl;

R is selected from

- H, C₁-C₅-alkyl, phenyl, C₁-C₅-phenylalkyl, C₁-C₅-cycloalkyl, C₁-C₅-alkenyl, C₁-C₅-alkoxy;
 - a residue of formula $-(CH_2)_n-NR_aR_b$ wherein n is an integer from 0 to 5 and each R_a and R_b, which may be the same or different, are C₁-C₆-alkyl, C₁-C₆-alkenyl or, alternatively, R_a and R_b, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II),



(II)

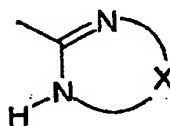
wherein W represents a single bond, O, S, N-R_c, R_c being H, C₁-C₆-alkyl or C₁-C₆-alkylphenyl.

R' is H, CH₃, CH₂CH₃;

R and R' can alternatively, form a heterocycle from 5 to 7 members of formula (III),

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(III)

wherein X represents a residue $-\text{O}(\text{CH}_2)_n-$ wherein n is an integer from 1 to 3, or a residue $-(\text{CH}_2)_n-$ wherein n is an integer from 2 to 4, or the ethylene residue $-\text{CH}=\text{CH}-$.

2. Compounds according to claim 1 selected from:

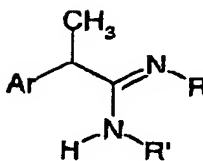
- (R,S) 2-(4-isobutylphenyl)propionamidine hydrochloride
- (+) 2-(4-isobutylphenyl)propionamidine hydrochloride
- (-) 2-(4-isobutylphenyl)propionamidine hydrochloride
- (R,S) 2-(3-benzoylphenyl)propionamidine hydrochloride
- (R,S) 2-[(3-fluoro-4-phenyl)phenyl]propionamidine hydrochloride
- (R,S) 2-(4-trifluoromethanesulfonyloxyphenyl)propionamidine hydrochloride
- (R,S) 2-(5-benzoyl-2-thiophene)propionamidine hydrochloride
- (R,S) 2-(4-isobutylphenyl)-N-[3'-(N'-piperidino)propyl]propionamidine dihydrochloride
- (R,S) 2-(4-isobutylphenyl)-N-methyl-propionamidine hydrochloride
- (R,S) 2-(3-benzoylphenyl)-N-[3-(N,N-dimethylamino)propyl]propionamidine hydrochloride
- (R,S) 2-(4-isobutylphenyl)propionamidine acetate salt
- (R,S) 2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl] propionamidine
- (R,S) 2-(4-isobutylphenyl)-N-benzyl propionamidine
- (R,S) 3-[1-(4-isobutylphenyl)ethyl]-5,6-dihydro-2H-1,2,4-oxadiazine
- (R,S) 2-[1-(4-isobutylphenyl)ethyl]-4,5-dihydro-2H-1,3-imidazole.

3. Compounds according to claims 1 or 2, for use as medicaments.

- 4. Use of compounds according to claims 1 or 2 in the preparation of a medicament for the treatment of diseases that involve the chemotaxis of human PMNs induced by interleukin-8.
- 5. Use of compounds according to claims 1 or 2 in the preparation of a medicament for the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigo, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.
- 6. Pharmaceutical compositions comprising a compound according to claims 1 or 2 in admixture and a suitable carrier thereof.

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7. Use of amidines of formula (I)



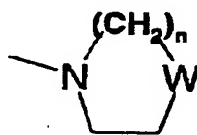
(I)

and pharmaceutically acceptable salts thereof,

wherein Ar is a phenyl group non-substituted or substituted by one or more groups independently selected from halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, hydroxy, C₁-C₄-acyloxy, phenoxy, cyano, nitro, amino, C₁-C₄-acylamino, halogen-C₁-C₃-alkyl, halogen C₁-C₃-alkoxy, benzoyl or a substituted or unsubstituted 5-6 membered heteroaryl ring selected from pyridine, pyrrole, thiofene, furane, indole.

R is selected from

- H, C₁-C₅-alkyl, phenyl, C₁-C₅-phenylalkyl, C₁-C₅-cycloalkyl, C₁-C₅-alkenyl, C₁-C₅-alkoxy;
- a residue of formula $-(CH_2)_n-NR_aR_b$ wherein n is an integer from 0 to 5 and each R_a and R_b, which may be the same or different, are C₁-C₆-alkyl, C₁-C₆-alkenyl or, alternatively, R_a and R_b, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II),



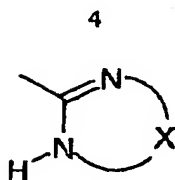
(II)

wherein W represents a single bond, O, S, N-R_c, R_c being H, C₁-C₆-alkyl or C₁-C₆-alkylphenyl.

R' is H, CH₃, CH₂CH₃.

R and R' can alternatively, form a heterocycle from 5 to 7 members of formula (III),

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(III)

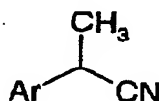
wherein X represents a residue $-O(CH_2)_n-$ wherein n is an integer from 1 to 3, or a residue $-(CH_2)_n-$ wherein n is an integer from 2 to 4, or the ethylene residue $-CH=CH-$ in the preparation of a medicament for the treatment of diseases that involve the chemotaxis of human PMNs induced by interleukin-8.

8. Use of compounds according to claim 7, wherein R is selected from
- hydrogen

- a residue of formula $-(CH_2)_n-NR^aR^b$, wherein n is an integer from 2 to 3 and the group Nr^aR^b is selected from N,N-dimethylamine or 1-piperidyl, and R^a is H, or R^a and R^b form a heterocycle of formula (III), where X represents a residue $-O(CH_2)_n-$ wherein n is the integer 1 or 2, or a residue $-(CH_2)_2$.

9. Use of compounds according to claims 7 or 8 in the preparation of a medicament for the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigo, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

10. Process for the preparation of compounds of formula (I) according to claim 1 comprising the reaction of a nitrile derivate of formula (IV),



(IV)

wherein Ar has the same meaning as defined in claim 1, with an amine of formula NHR , wherein R has the same meaning as defined in claim 1.

11. Process for the preparation of compounds of formula (I) according to claim 1, wherein R and R' groups form an heterocycle of formula (III), comprising the reaction of amidines of formula (I) wherein R' is H and R is H or OH, with a reagent of formula $L-K-L'$, in the presence of a base, wherein L and L' are leaving groups, and, when R and R' are both H, K

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represents a residue $-(CH_2)_n-$ wherein n is an integer from 2 to 4; when R is OH and R' is H ,
 K represents a residue $-(CH_2)_n-$ wherein n is an integer from 1 to 3.

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